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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER
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ART UNIT	PAPER NUMBER
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1623  
DATE MAILED:

16  
04/22/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

# Office Action Summary

Application No.

09/032,972

Applicant(s)

Krotz et al.

Examiner

L. E. Crane

Group Art Unit

1623

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ----3---- MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

## Status

- ☒ Responsive to communication(s) filed on 9/7/00 (CPA and IDS)
- ☒ This action is **FINAL**.
- ☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

## Disposition of Claims

- ☒ Claim(s) 1-41 is/are pending in the application.  
Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- ☒ Claim(s) 1-41 is/are rejected.
- ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- ☐ Claim(s) \_\_\_\_\_ are subject to restriction or election requirement.

## Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.
- ☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119 (a)-(d)

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
  - ☐ All ☐ Some\* ☐ None of the CERTIFIED copies of the priority documents have been received.
  - ☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_
  - ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

## Attachment(s)

- ☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 15 ☐ Interview Summary, PTO-413
- ☒ Notice of Reference(s) Cited, PTO-892 ☐ Notice of Informal Patent Application, PTO-152
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948 ☐ Other \_\_\_\_\_

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The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group 1600, Art Unit 1623.

5        No claims have been cancelled or amended. The Continued Prosecution Application (CPA) petition has been received and entered. An Information Disclosure Statement (IDS), four references, and a PTO-1449 citing two references have been received along with two other references. One of the two un-cited references has been made of record on a PTO-892, 10 but the other is incomplete (2 un-numbered pages from Current Protocols in Nucleic Acid Chemistry, no volume, year, page numbers, author(s), etc.) and therefore presently cannot be made of record.

Claims 1-41 remain in the case.

15        The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

20        "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made."

25        Claims 1-41 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ravikumar '621 (PTO-892 ref. A) in view of Caruthers et al. '679 (PTO-892 ref. G) and further in view of Froehler et al. '076 (PTO-892 ref. H) and further in view of Sproat et al. (PTO-892 ref. W), Conway et al. (PTO-892 ref. Y), Atkinson et al. (PTO-892 ref. Z), and Sproat et al. (PTO-892 ref. RA).

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The instant claims are directed to entirely conventional oligonucleotide syntheses wherein the only variation from the prior art is the choice of solvent or solvent mixture present for deprotection step (c).

5        Ravikumar '621 (PTO-892 ref. A) discloses entirely conventional oligonucleotide synthesis wherein the solvent for the coupling step is acetonitrile in the examples and the P-protecting group varies from the conventional phosphorus-ester protecting group. At column 10, lines 1-16, this reference makes a generic disclosure of the process steps leading to an  
10        oligonucleotide, including acid-mediated deprotection of the 5'-hydroxyl moiety of a solid-support-attached nucleoside. However, no disclosure of preferred solvent for the required acid reagent is included. In the same column at line 50, the removal of 5'-hydroxyl protection by contact with acid from a solid-support-attached oligonucleotide is also taught without specifying any particular solvent. At column 14, lines 5-28, a more  
15        complete disclosure of possible 5'-hydroxyl protecting groups is provided along with a list of acids effect to deprotect, but no preferred solvents are listed. At column 18, lines 37-41, deprotection is accomplished by contact with a solution of dichloroacetic acid in dichloromethane, conditions repeated in subsequent experimental procedures. The choice of any  
20        particular deprotection solvent is therefore apparently a choice within the purview of the ordinary practitioner in view of this disclosure. This reference does not disclose the particular mixture of solvents selected for use in the instant claimed processes.

25        Caruthers et al. '679 (PTO-892 ref. G) at column 5, lines 10-14, teaches the use of "... any solvent which will dissolve the reactants ..." including a list of specific organic solvents for phosphoramidite-intermediate-based oligonucleotide synthesis. The context of this statement suggests that

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Caruthers was making reference to the coupling step. However, the same generic teaching appears to also apply to the deprotection step where four different solvent/reagent systems were disclosed by Caruthers as effective in the

5 5'-O-detritylation process:

(1) see column 16, Table IV, footnote 1 (ZnBr<sub>2</sub> in nitromethane);

(2) see column 16, Table V, footnote 1 (toluenesulfonic acid in chloroform:methanol (7:3));

10 (3) see column 18, lines 26-28 (ZnBr<sub>2</sub> in nitromethane:methanol (19:1));  
and

(4) see column 19, lines 47-50 (80% acetic acid).

This reference does not disclose the particular mixture of solvents selected for use in the instant claimed processes.

15 Froehler et al. '076 (PTO-892 ref. H) discloses the use of H-phosphonate intermediates for the coupling step in the synthesis of oligonucleotides and phosphorothioate analogues thereof. This reference also teaches the use of "... an anhydrous organic solvent, preferably pyridine/acetonitrile ...," at column 5, lines 26-28. This "what ever works best" philosophy apparently also applies to the deprotection step; see  
20 column 5, lines 38-47. The last line of this portion of column 5 is particularly instructive. After listing 3 (three) different deprotection reagent/solvent mixtures, Froehler suggests a very flexible "whatever works" approach by further stating that "[o]ther deprotection procedures suitable for other known protecting groups will be apparent to the  
25 ordinary practitioner." This reference does not disclose the particular mixture of solvents selected for use in the instant claimed processes.

Sproat et al. (PTO-892 ref. W) discloses at p. 52, (lines 2 and 18) that toluene is useful for the purification of synthetic nucleoside intermediates.

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5 Additionally, this reference discloses at pp. 64 (Protocol 17, step 3) and page 70 (Protocol 25, step 4) that benzene is a solvent for key oligonucleotide synthesis reagents and for nucleoside-3'-O-phosphoramidites, and may be used to co-evaporate triethylamine therefrom.

10 Conway et al. (PTO-892 ref. Y) is directed to the chemical synthesis of labeled DNA and at p. 218, Section C, Subsection 2, discloses the specific use of toluene as an effective solvent for dissolution of pyridine-contaminated dinucleoside monophosphorothioate d[Cp(s)C] prior to co-evaporative removal of the pyridine/toluene mixture therefrom. The instant reference does not disclose that toluene is used in the coupling step required to make this compound.

15 Atkinson et al. (PTO-892 ref. Z) discloses at p. 43 in section (xvii), that toluene is useful to dissolve the 3'-O-phosphoramidites of 2'-deoxyadenosine, 2'-deoxycytidine, and 2'-deoxyuridine as the first step in a re-precipitation or recrystallization process. This reference also teaches at p. 76, section 7.5, "Variation in Procedures," although no specific teaching of the substitution of an aromatic solvent from other solvents used in oligonucleotide synthesis is present in this section. In section 8.7 at p. 80, "toluene" is listed as a reagent useful in the preparation of "Deoxyribonucleoside-derivatized supports." This reference at the noted locations does not disclose the particular set of solvents claimed herein as useful in the coupling step of an oligonucleotide synthesis.

25 Sproat et al. (PTO-892 ref. RA) at p. 84, lines 10 and 9 from the end of the page, discloses that the "[p]urity of solvents and reagents is of the utmost importance as far as reliability and reproducibility of the

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[oligonucleotide synthetic] method are concerned." This reference also discloses at p. 93, section (xv), that a di-protected adenosine derivative may be effectively dissolved in toluene prior to evaporative solvent removal for the purpose of co-evaporating residues of pyridine therefrom (see also p. 96, section (vi) for a similar disclosure). Additionally, at p. 111, section 7.6, the listing of solvents useful in oligonucleotide synthesis includes both benzene and toluene. This reference at the noted locations does not disclose the particular set of solvents claimed herein as useful in the coupling step of an oligonucleotide synthesis.

The teachings of the prior art Caruthers and Froehler references motivate the selection of practically any organic solvent or solvent mixtures which will dissolve the reactants and not otherwise interfere with the intended synthetic transformation. The first three references provide descriptions of conventional prior art processes for making oligonucleotides via phosphoramidite or H-phosphonate intermediates including the 5'-O-deprotection process step. The noted portions of the Caruthers and Froehler both teach that the choice of a particular solvent or solvent mixture is a variable clearly within the purview of the ordinary practitioner. The Sproat et al. (W), Conway et al., Atkinson et al., and Sproat et al.(RA) references are each generally directed to oligonucleotide synthesis thereby providing proper motivation to combine with the primary references. The secondary references provide disclosures that at least two different nucleoside-3'-O-phosphoramidites, at least one dinucleotide derivative, and some other nucleoside derivatives may be effectively dissolved in the aromatic hydrocarbon solvents benzene and/or toluene. These disclosures are deemed to provide factually specific motivations for the ordinary practitioner conducting routine experimentation to substitute toluene, benzene, or their closely related aromatic solvent relatives as substitutes for at least a portion of the

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solvents typically used during the deprotection step in oligonucleotide synthesis. For these reasons the instant process claims are deemed to be lacking in any patentable distinction in view of the noted prior art.

5 Therefore, the instant claimed oligonucleotide processes would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

Applicant's arguments filed May 12, 2000 have been fully considered but they are not persuasive.

10 Applicant argues that the prior art of record fails to motivate the instant claimed invention as an obvious variation of well established process art. In particular applicant argues that the prior art does not suggest the choice of solvent for the process steps where solvent variation has been introduced as an improvement by applicant. Quoting the "Gait reference" (examiner presumes applicant refers to PTO-892 ref. V)

15 applicant argues that small variations in oligonucleotide synthesis are much more sensitive to variations in process conditions than biochemical processes and that solvent variations can severely impact product yield. Applicant then notes that Ravikumar specifies methylene chloride solvent and notes that Caruthers et al. '679 teaches the use of "any solvent which

20 will dissolve the reactants," arguing that such a statement ignores the effect such a choice may have on reaction yield. After noting that secondary references Sproat (W), Atkinson, Conway and Sproat (RA) fail to disclose the use of toluene in a process step, applicant concludes that there is no motivation to combine and therefore the claims should be found

25 allowable. Examiner respectfully disagrees.

Applicant's argument fails to provide specific examples of what constitutes an inappropriate solvent choice. Applicant quotes comparisons



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of vastly different arts (biochemical synthesis vs. chemical synthesis) and then suggests reliance on the conclusion that small changes in chemical synthesis conditions are much more sensitive to change than parallel changes in biochemical conditions. This comparison is based on the

5 premise that the ordinary practitioner of biochemical arts is comparable to the ordinary practitioner of chemical oligonucleotide synthesis, a premise which is incorrect and therefore is inapplicable in the instant context as being beside the point. Applicant's arguments attempt to dispense with the clear teachings of the Caruthers reference (e.g. "any solvent which will

10 dissolve the reactants" is an appropriate choice) without noting the context of the quotation. Caruthers '679 clearly teaches at column 5, lines 8-22 that "[t]he reaction proceeds smoothly at room temperature in a dry atmosphere and under an inert gas," then goes on to list solvents which work including chlorinated compounds, a carboxylic acid ester, cyclic and

15 straight chain ethers " ... and the like." The phrase "... and the like" is deemed to be nothing less than a failure to narrowly limit solvent choice, and also a suggestion that many other aprotic solvents can be expected to work as substitutes. The Froehler et al. '076 reference also supports this view at column 5, lines 26-28 and lines 37-51 wherein terms like "an

20 anhydrous organic solvent" teach that the condition of the solvent (anhydrous) is important but that the choice of a particular solvent is not critical, implying that the choice of any particular solvent is open to the ordinary practitioner conducting routine experimentation. These quotes taken from the references cited in the rejection of record are deemed to be

25 a further basis for motivating the ordinary practitioner to seek alternative solvents. Therefore, citation of the secondary references is deemed to have been properly motivated and the choices provided therein appropriate as possible alternative or substitute solvents.

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Examiner therefore concludes that applicant's argument, based on selected quotes taken individually and taken as a whole, is not a proper or convincing basis for withdrawal of the instant grounds of rejection. Therefore, the instant ground of rejection has been maintained.

5        Addendum in response to references newly made of record at the time of this Office action: the PTO-1449 cites and the PTO-892 cite are all relevant, but do not provide any convincing basis for a finding of patentable distinction. Rather, they each suggest that the instant claimed process variation is little more than one of many different attempts to  
10       solve the problem of depurination associated with acid-mediated detritylation, no one of which really overcomes this technical limitation.

15       This is a CPA of applicant's earlier application S.N. 09/032,972. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds or art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP §706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. §1.136(a). The practice of automatically extending the shortened statutory period an additional  
20       month upon the filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

25       A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD

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WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY  
EXTENSION FEE PURSUANT TO 37 C.F.R. §1.136(a) WILL BE CALCULATED  
FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL  
THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS  
5 FROM THE DATE OF THIS FINAL ACTION.

Papers related to this application may be submitted to Group 1600 via  
facsimile transmission(FAX). The transmission of such papers must  
conform with the notice published in the Official Gazette (1096 OG 30,  
November 15, 1989). The telephone numbers for the FAX machines  
10 operated by Group 1600 are **(703) 308-4556** and **703-305-3592**.

Any inquiry concerning this communication or earlier communications  
from the examiner should be directed to Examiner L. E. Crane whose  
telephone number is **703-308-4639**. The examiner can normally be  
reached between 9:30 AM and 5:00 PM, Monday through Friday.

15 If attempts to reach the examiner by telephone are unsuccessful, the  
examiner's supervisor, Mr. Gary Geist, can be reached at **(703)-308-1701**.

Any inquiry of a general nature or relating to the status of this  
application should be directed to the Group 1600 receptionist whose  
telephone number is **703-308-1235**.

20 LECrane:lec  
09/19/00



GARY GEIST  
SUPERVISORY PATENT EXAMINER  
TECH CENTER 1600